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Neurobiological alterations in PTSD: implications for pharmacotherapy

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> Drugs should have no part in psychotherapeutics: tonics are unnecessary, the virtue of valerian is a superstition, a placebo is anathema, and the use of bromides not only rests upon heresy, but is physically and mentally harmful. Even aperients must be allowed sparingly, for constipation is a part of the disease, and disappears with the other symptoms.
>
> (Culpin, 1920, p. 177)

Many would still agree with the nihilism expressed by Millais Culpin in 1920 regarding his pharmacotherapeutic experience with war-related 'functional nerve disease' among British military patients. It is certainly clear that no drug has yet emerged as the treatment of choice for contemporary trauma survivors who suffer from post-traumatic stress disorder (PTSD). My task is to review our current state of knowledge and to determine whether we have reason to be more optimistic about pharmacotherapy for this disorder than Dr Culpin was.

PTSD is associated with significant abnormalities in a number of neurobiological systems. As we learn more about the pathophysiology of this disorder, we are encouraged to believe that pharmacological interventions may have an important place in the routine treatment of PTSD. Unfortunately, research on clinical pharmacology has not kept pace with basic research. There are few solid findings from clinical outcome studies to guide clinicians regarding the choice of drug, optimal dose or necessary duration of treatment. Despite such significant gaps in the literature, many experienced clinicians are convinced that medication is useful. A number of practical questions have emerged from the collective treatment experience of practising pharmacotherapists. Is there a single best drug for PTSD? Is it appropriate to consider using several drugs concurrently? Are there contra-indications for certain medications? Are there concerns about side-effects that are specific for PTSD patients? In this chapter, I will address each of these issues from the perspective of a practising clinician. First, I will present some of the most pertinent findings regarding the neurobiology of PTSD. Next, I will review the scientific literature concerning clinical pharmacology. Finally, I will discuss practical issues pertaining to pharmacotherapy for PTSD.

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NEUROBIOLOGY

Many of the neurobiological mechanisms involved in normal coping and adaptation appear to be altered in PTSD. This is especially true of the catecholaminergic and hypothalamic–pituitary–adrenocortical (HPA) systems, both of which are perched atop a complex cascade of interacting neurotransmitter, neuroendocrine and psychoimmunological mechanisms. Stress-induced dysregulation of adrenergic and HPA activity is often associated with abnormalities in thyroid, opioid, serotonergic, dopaminergic, immunological and other systems (Chrousos and Gold, 1992). A thorough review of the psychophysiological and neurobiological abnormalities listed in Table 1 is beyond the scope of this chapter. The reader is referred to several books and reviews that address this topic much more thoroughly (Giller, 1990; Friedman, 1991; Charney et al, 1993; Murburg, 1994; Friedman et al, 1995). In my abbreviated review of the neurobiology of PTSD, I will focus on neurotransmitter abnormalities for which certain drugs or classes of drug are currently available. Therefore, I will concentrate on adrenergic, dopaminergic and serotonergic mechanisms in PTSD and will also touch upon possible alterations in opioid, GABA–benzodiazepine and *N*-methyl-D-aspartate (NMDA) function. Other biological abnormalities appear to be more important from a differential diagnostic rather than a therapeutic perspective. Since they may have significant implications regarding choice of drug or treatment strategy, they will also be included in this review.

Table 1. Neurobiological alterations in PTSD.

1.	Heightened sympathetic reactivity
2.	Excessive adrenergic activity
3.	HPA axis abnormalities
4.	Elevated thyroid function
5.	Opioid system dysregulation
6.	Exaggerated startle response
7.	Disturbed sleep and dreaming
8.	Possible serotonergic abnormalities
9.	Possible dopaminergic abnormalities
10.	Possible sensitization of limbic nuclei (with GABA–benzodiazepine and/or NMDA abnormalities)
11.	Possible immunological abnormalities

Catecholamines

Most of the abnormalities shown in Table 1 have been detected among American or Israeli male military veterans with PTSD. More recent work on male and female survivors of other traumas (such as sexual assault, accidents or the Nazi Holocaust) has confirmed these original findings, suggesting that they may be generalizable to all PTSD patients. Catecholaminergic dysregulation is indicated by heightened sympathetic reactivity and excessive adrenergic activity. PTSD patients exhibit greater

cardiovascular, electrodermal and electromyographic reactivity when exposed to trauma-related stimuli. This response can be reliably evoked by a variety of auditory, visual and olfactory stimuli that bear some relationship to the original trauma. In the case of Vietnam veterans, for example, heightened sympathetic reactivity can be evoked by exposure to the sounds, sights and smells of their combat experience in Vietnam (Blanchard et al, 1982; Malloy et al, 1983; Pitman et al, 1987). Similar findings have been obtained with PTSD patients who have survived motor vehicle accidents (Blanchard et al, 1991), Israeli survivors of non-combat trauma (Shalev et al, 1993) and adult female survivors of childhood sexual abuse (Orr et al, 1993). Furthermore, it has been shown that such sympathetic reactivity in response to trauma-related stimuli is also associated with acute elevations in plasma norepinephrine levels (McFall and Murburg, 1994).

Additional evidence for increased adrenergic activity in PTSD comes from elevated 24-hour urinary catecholamine levels among Vietnam veterans and survivors of the Nazi Holocaust (Giller et al, 1990; Yehuda et al, 1994), downregulation of adrenergic α_2- and β-receptors (Lerer et al, 1990; Perry et al, 1990) and unique sensitivity to the selective noradrenergic α_2-antagonist yohimbine (Southwick et al, 1993). Yohimbine, a drug that produces noradrenergic activation in the brain through disinhibition of the locus coeruleus, produces panic attacks and Vietnam-related flashbacks in war veterans with PTSD. Although yohimbine can also trigger panic attacks in patients with panic disorder, it has no such effect on normal controls. A much more extensive review of catecholamine function in PTSD can be found in Michele Murburg's (1994) recent book, devoted entirely to this topic.

Before leaving the review of catecholamines, it should be noted that a few studies indicate that there are also dopaminergic abnormalities in PTSD patients. Significant elevations in urinary homovanillic acid (the major metabolite of dopamine) are found in both Vietnam veterans and Nazi Holocaust survivors with PTSD (Yehuda et al, 1994). Vietnam veterans with PTSD also exhibit elevated plasma dopamine levels (Hamner and Diamond, 1994). Recent rape victims show greatly increased urinary conjugated dopamine levels (Ende et al, 1990), and physically abused boys show abnormal sensitivity with regard to the growth hormone response to L-dopa (Jensen et al, 1991). Animal studies have suggested dopamine involvement in the stress response (Zacharko, 1994; Deutch and Young, 1995; Sorg and Kalivas, 1995).

Serotonin

In contrast to the growing literature on catecholaminergic abnormalities in PTSD, very little research has explored other neurotransmitter systems. Serotonergic (5-HT) mechanisms are especially interesting because of the recent emergence of specific serotonin re-uptake inhibitors (SSRIs) as first-line drugs in the treatment of affective and anxiety disorders. Furthermore, 5-HT is implicated in a number of diverse anxiety reactions (Gonzalez-Heydrich and Peroutka, 1990).

Finally, serotonergic mechanisms are thought to mediate a number of symptoms or syndromes frequently associated with PTSD, such as impulsivity, aggressiveness, suicidal behaviour, alcoholism, substance abuse, depression and personality disorders (Yager, 1976; Penk et al, 1981; Yager et al, 1989; Carol et al, 1985; Cloninger, 1987; see Friedman, 1990, for additional references).

Serotonin-related abnormalities among PTSD patients have only been reported in two preliminary studies. Southwick et al (1991) reported that the 5-HT agonist *m*-chlorophenylpiperazine (MCPP) produced panic attacks and trauma-related dissociative episodes and flashbacks among Vietnam veterans with PTSD. No such reaction was elicited by placebo; furthermore, non-PTSD Vietnam veterans failed to respond to MCPP. In a second study, Corrigan et al (1990) administered clomipramine (a tricyclic anti-depressant that promotes 5-HT activity through an SSRI-like action) to adult female survivors of childhood sexual abuse. In contrast to a control group, the traumatized women exhibited blunting of both the prolactin and cortisol responses to intravenous clomipramine.

Opioid, GABA–benzodiazepine and NMDA mechanisms

A number of animal models have been proposed for PTSD, including fear conditioning, failure in extinction, sensitization and inescapable stress. Neurotransmitter systems not mentioned previously that are involved in some of these phenomena include opioid, GABA–benzodiazepine and NMDA mechanisms (van der Kolk, 1985; Southwick et al, 1992; Bremner et al, 1993; Charney et al, 1993). There is little research on human patients with PTSD that is relevant to these animal models. Altered opioid function among PTSD patients is suggested by naloxone-reversible elevations in pain thresholds following exposure to trauma-related stimuli (Pitman et al, 1990), lowered pain thresholds at other times (Perry et al, 1987) and abnormalities in enkephalin metabolism (Wolf et al, 1990). Indirect arguments suggesting possible alterations in GABA–benzodiazepine function are: (a) benzodiazepine inverse agonists can produce panic and anxiety in normal subjects (Dorrow et al, 1983); (b) benzodiazepine receptor antagonists can precipitate panic attacks in patients with panic disorder but not in normal controls (Nutt et al, 1990; Woods, 1991); and (c) limbic kindling (see below) is associated with increased benzodiazepine receptor binding (McNamara et al, 1985). Finally, NMDA mechanisms appear to play an important role in the learning abnormalities postulated to occur in PTSD, such as fear conditioning, altered extinction and sensitization (Charney et al, 1993). With regard to the latter, kindling and behavioural sensitization of limbic structures have been postulated as neurobiological mechanisms that might account for the long-term alterations in brain function that appear pertinent to PTSD (Lipper et al, 1986; Post et al, 1995). If valid, this would suggest that anti-kindling agents or other drugs that affect NMDA function might have a useful role in the pharmacotherapy of PTSD.

The hypothalamic–pituitary–adrenocortical axis

Other PTSD-related abnormalities shown in Table 1 above currently appear more important from a diagnostic rather than from a therapeutic perspective. We (Friedman and Yehuda, 1995) have recently reviewed psychobiological approaches to differential diagnosis. We conclude that altered HPA function is one of the most important aetiological and diagnostic abnormalities observed in PTSD patients. In contrast to patients with major depressive disorder (MDD), who exhibit excessive HPA activity and cortisol non-suppression during the dexamethasone suppression test (DST), PTSD patients exhibit reduced HPA activity and super-suppression during DST (Yehuda et al, 1993, 1995). Because PTSD patients frequently meet diagnostic criteria for MDD, the major potential advantage of the DST is to distinguish PTSD from MDD, since the direction of HPA change is virtually opposite in these two disorders. Furthermore, the fact that DST super-suppression is often found in patients who meet diagnostic criteria for both PTSD and MDD suggests that the MDD associated with PTSD may represent a neurobiological abnormality different from MDD not associated with PTSD. The promise of DST in this regard may have important prognostic implications for patient identification for pharmacotherapy.

Thyroid function, startle reflex and sleep

In addition to HPA dysregulation, PTSD patients exhibit alterations in thyroid function, the acoustic startle eyeblink reflex, sleep physiology and probably immunological function. In contrast to control groups, Vietnam veterans with PTSD exhibit increased mean serum total thyroid (T4), thyroid-binding globulin, total and free triiodothyronine (T3), and higher T3/T4 ratios. Sometimes, these elevated thyroid indices are at or near the thyrotoxic range (Mason et al, 1995). PTSD patients also exhibit an exaggerated startle response, as manifested by shorter latency, greater amplitude and significant loss of normal inhibitory modulation of the startle reflex (Howard and Ford, 1992; Shalev et al, 1992; Ornitz and Pynoos, 1989). A third abnormality is disruption of normal sleep and dreaming, manifested by increased sleep latency, decreased sleep time, increased awakenings, increased nocturnal movements and possible alterations in sleep architecture. Furthermore, traumatic nightmares appear to be unique events that differ from classic nightmares occurring during stage 4 or REM sleep (Friedman, 1981; Ross et al, 1989, 1994; Woodward, 1995). Finally, extrapolating from the stress and health literature that shows suppression of immunological function in response to normal stress (Cohen and Williamson, 1991; Chrousos and Gold, 1992; Kiecolt-Glaser and Glaser, 1992), there is every reason to expect that traumatic stress will also impair immunological capability. We (Friedman and Schnurr, 1995) have speculated that such immunological deficits might account, in part, for the adverse medical outcomes seen in patients with PTSD.

PSYCHOPHARMACOLOGY

Before reviewing the efficacy of specific drugs, it is necessary to comment on the status of the general literature on clinical pharmacology for PTSD. Progress has been slow. Despite numerous open trials and case reports, there are only eight controlled drug trials that have been published. In our summary of the literature on randomized clinical trials (RCTs), we (Friedman and Southwick, 1995) observed: (a) with one exception (phenelzine), no drug has been tested more than once; (b) dose and duration of treatment have not been systematically controlled; (c) co-morbid diagnoses often associated with PTSD have not been adequately controlled; (d) instrumentation used to assess treatment outcome has not always been optimal; and (e) since most studies to date have been conducted on Vietnam veterans with PTSD, future drug trials must include male and female patients from different ethnocultural backgrounds who have been exposed to traumatic events besides war (such as sexual assault, natural disasters, torture or accidents). These remarks should not be interpreted as an argument against drug treatment for PTSD. Instead, they should be understood as an argument for more research.

Drugs affecting adrenergic mechanisms

Given the excessive adrenergic activity observed among PTSD patients, it might be expected that symptom relief could be achieved with drugs that reduce such activity. Information is available on the efficacy of two pharmacological agents that suppress adrenergic function through different mechanisms. These are the α_2-adrenergic agonist clonidine, and the post-synaptic β-adrenergic blocking agent propranolol.

Three open trials with clonidine have been promising. Kolb et al (1984) observed reductions in traumatic nightmares, intrusive recollections, hypervigilance, insomnia, startle reactions and angry outbursts among Vietnam veterans with PTSD. Perry (1994) reported that children with PTSD showed reduced impulsivity, anxiety and arousal, as well as improved mood and concentration following clonidine treatment. Finally, Kinzie and Leung (1989) found, among Cambodian refugees with PTSD, that a clonidine/imipramine combination produced a greater reduction in PTSD nightmares, startle reactions and insomnia than did either drug alone. There have been no RCTs with clonidine.

Two out of three trials with propranolol have also had positive results. Propranolol successfully reduced intrusive and arousal PTSD symptoms in Vietnam veterans with PTSD (Kolb et al, 1984) and in children with PTSD who had been exposed to physical or sexual abuse (Famularo et al, 1988). On the other hand, propranolol was not effective with Cambodian refugees (Kinzie and Leung, 1989). The study with abused children is particularly noteworthy since it was an A–B–A design (6 weeks off–6 weeks on–6 weeks off medication), in which significant symptom reduction occurred during propranolol treatment; there was a return to pre-treatment severity

of PTSD symptoms after propranolol was discontinued. There have been no RCTs with propranolol.

Tricyclic anti-depressants and monoamine oxidase inhibitors

Tricyclic anti-depressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are the most extensively tested drugs in PTSD patients. Given the overlapping symptomatology and co-morbidity between PTSD and depression on the one hand, and PTSD and anxiety disorders on the other (see Friedman and Yehuda, 1995), it is no wonder that TCAs and MAOIs have attracted so much attention. Furthermore, the anxiolytic and anti-panic properties of TCAs and MAOIs are at least partially related to their action on adrenergic mechanisms (Sheehan et al, 1980; Charney et al, 1981; Kahn et al, 1986). It is also important to note in this regard that both TCAs and MAOIs additionally potentiate serotonergic activity.

Southwick et al (1994) reviewed all 15 published reports (case reports and open trials, as well as RCTs) in which anti-depressants were used to treat PTSD. They evaluated the efficacy of TCAs and MAOIs on each of the three PTSD symptom clusters (re-experiencing, avoidant and hyperarousal), on depressive symptoms and on anxiety/panic symptoms. Their analysis indicated that both classes of anti-depressants produced moderate-to-marked improvement in 75% of patients. Global response was judged moderate-to-good for 82% of MAOI patients and 45% of TCA patients. Improvement was limited, however, to a reduction in re-experiencing symptoms such as intrusive recollections, traumatic nightmares and PTSD flashbacks. Insomnia was also reduced. Otherwise, PTSD avoidant, hyperarousal, depression and anxiety/panic symptoms all failed to respond to either class of anti-depressant.

The five published RCTs with anti-depressants have produced mixed results. Excellent reduction in intrusive symptoms was found in one study with both the MAOI phenelzine and the TCA imipramine (Frank et al, 1988; Kosten et al, 1991) following 8 weeks of treatment. A 4-week trial with phenelzine (Shestatzky, et al, 1988), and a 4-week trial with the TCA desipramine (Reist et al, 1989), showed no difference between active drug and placebo groups. Finally, an RCT with amitriptyline (Davidson, et al, 1990) demonstrated a small reduction in avoidant but not intrusive symptoms.

Although more research with anti-depressants is clearly needed, results from both the quantitative analysis and RCTs suggest that adequate clinical trials with TCAs or MAOIs (and probably with other drugs as well) must last a minimum of 8 weeks. Second, these results suggest that successful treatment with anti-depressant drugs may only ameliorate intrusive symptoms and not reduce PTSD avoidant or arousal symptoms.

Drugs affecting serotonergic mechanisms

Given the success of SSRIs in depression, panic and obsessive–compulsive disorder, it is not surprising that publications have begun to appear

extolling their efficacy in PTSD. Currently, six reports (including one RCT) have appeared regarding SSRIs in PTSD. In contrast to investigations with TCAs and MAOIs, which have mostly been restricted to male Vietnam veterans, studies with SSRIs have included men and women exposed to civilian trauma (sexual assault, motor vehicle/industrial accidents, etc.) and Second World War Dutch resistance fighters, as well as Vietnam veterans with PTSD. A second difference between other anti-depressants and SSRIs concerns their spectrum of action. Whereas TCAs and MAOIs appear to produce their major effort on PTSD re-experiencing symptoms, SSRIs produce reductions in avoidant/numbing symptoms. They appear to be the first class of drug to exhibit such an effect. Some reports indicate that SSRIs also ameliorate re-experiencing and/or arousal symptoms of PTSD.

In the only published RCT (van der Kolk et al, 1994), fluoxetine successfully reduced overall PTSD symptomatology, especially with respect to numbing and arousal symptoms. The data suggest that these actions were completely unrelated to fluoxetine's anti-depressant effect. These results also suggest that responsivity to medication may, in part, be a function of severity, chronicity and co-morbid diagnoses, since civilian childhood abuse survivors had a much better response than did Vietnam veterans with PTSD.

Similar findings have been recorded with fluoxetine and fluvoxamine in open trials and case reports (Davidson et al, 1991; De Boer et al, 1992; Nagy et al, 1993; see Friedman and Southwick, 1995, for additional references). Sertraline has also reduced PTSD symptoms in Vietnam veterans (Kline et al, 1994) and rape victims (Rothbaum et al, 1994). Clinical investigators have been most impressed by the amelioration of avoidant/numbing symptoms produced by SSRIs, since few other drugs have affected those symptoms. Further evidence that serotonergic mechanisms are somehow involved in avoidant/numbing symptoms comes from the observation that amitriptyline (the TCA with the most potent 5-HT action tested so far) is the only TCA to produce some reduction in avoidant/numbing symptoms. SSRIs may also produce improvement in other PTSD core symptoms, since some reports indicate that patients also exhibited reduced re-experiencing and arousal symptoms in addition to amelioration of avoidant/numbing symptoms. A number of problems frequently associated with PTSD are thought to be associated with serotonergic mechanisms (Yager, 1976; Penk, 1981; Yager et al, 1984; Carol et al, 1985; Cloninger, 1987; see Friedman, 1990, for additional references). These include rage, impulsivity, suicidal behaviour, aggression, depression, obsessive–compulsive symptoms, panic and behaviour associated with alcoholism and substance abuse. It is possible that such symptoms will also respond to SSRIs.

Reports on SSRIs have thus far been limited to fluoxetine (up to 80 mg daily), fluvoxamine (up to 300 mg daily) and sertraline (up to 200 mg daily). Investigations with other SSRIs can be expected in the future. As with TCAs and MAOIs, it appears that an adequate clinical trial of an SSRI will require 10–12 weeks.

Finally, brief reports have appeared concerning two non-SSRI drugs that also act on 5-HT systems; buspirone and cyproheptadine. Buspirone, a

5-HT_{1A} partial agonist that is an effective anxiolytic, produced reductions in anxiety, insomnia, flashbacks and depressed mood in three combat veterans with PTSD (Wells et al, 1991). Cyproheptadine, a 5-HT antagonist, has reportedly exhibited a selective action that suppresses recurrent traumatic nightmares without affecting other PTSD symptoms (Harsch, 1986; Brophy, 1991).

Benzodiazepines

Benzodiazepines are used widely in some clinical settings and sparingly elsewhere. Their proven anxiolytic potency makes them an understandable choice for use in an anxiety disorder such as PTSD. Indeed, in one clinical setting up to 71% of PTSD patients received benzodiazepines (Ciccone et al, 1988). On the other hand, given the high co-morbidity of alcoholism and substance abuse among PTSD patients (Kulka et al, 1990), many clinicians are reluctant to use benzodiazepines because they are afraid to prescribe such drugs to patients whom they regard as 'addictive prone'. We (Kofoed et al, 1993) have challenged this across-the-board anti-benzodiazepine bias. We argue that symptom reduction is the key to success in patients dually diagnosed with PTSD and alcoholism/substance abuse, and that benzodiazepines can play an important role in achieving symptom reduction in some of these patients. Therefore, we recommend that benzodiazepines be considered for use in carefully selected PTSD patients who will take the medication as prescribed and where the risk of further addiction seems less than the risk of untreated PTSD.

There are actually very few data that can be marshalled to support either side of this argument. In one open trial with alprazolam (Feldman, 1987), 16 out of 20 veterans with PTSD showed reduced insomnia, anxiety, irritability and hyperarousal. These are typical benzodiazepine effects, not necessarily specific to core PTSD symptoms, and it should be noted that four of these patients also exhibited benzodiazepine-induced emotional disinhibition, exemplified by increased outbursts of anger. A second study was an RCT with alprazolam in which the benzodiazepine was no more effective than placebo in reducing core PTSD symptoms (Braun et al, 1990). Finally, clonazepam successfully reduced insomnia, nightmares, flashbacks and panic attacks among PTSD patients who also suffered from multiple personality disorder (Lowenstein, 1991).

To summarize, it appears that benzodiazepines can ameliorate nonspecific anxiety, but there is little evidence that they have specific efficacy on core PTSD symptoms. Indications for benzodiazepine use appear to be: (a) in acute stress reactions when symptomatic anxiety reduction may forestall the later development of PTSD (see Friedman et al, 1993); (b) in chronic PTSD, among patients refractory to other drugs, when anxiety significantly interferes with the patient's capacity to participate in treatment (I would recommend episodic use of benzodiazepines for such patients); and (c) in PTSD patients with co-morbid alcohol or substance abuse who will take medication as prescribed. I suggest that, if benzodiazepine treatment seems necessary, clonazepam be the drug of choice because of its

efficacy, its low abuse potential, its safety and its anti-convulsant properties.

Anticonvulsants

One neurobiological model proposed for PTSD that has direct pharmacotherapeutic implications is a kindling/behavioural sensitization model (Post et al, 1995). Although kindling and behavioural sensitization are different phenomena that have different end-points and involve different neurobiological systems, they provide neurobiological mechanisms that account for the stability of PTSD over time. Both catecholamines and NMDA have been proposed as neurotransmitters that modulate such postulated sensitization of limbic nuclei following exposure to traumatic stress (Charney et al, 1993; Post et al, 1995). This model postulates that, following high-intensity traumatic exposure, limbic nuclei become increasingly sensitized to trauma-related stimuli. Following subsequent exposures, these limbic structures become progressively responsive to less intense stimuli. This is consistent with clinical observations that, following the initial traumatic event, PTSD patients exhibit marked responsivity to less intense stimuli, such as photographs depicting trauma-related images. Kindling (which in laboratory paradigms produce spontaneous seizures) has been invoked theoretically (by Post et al, 1995) to account for the spontaneous (in contrast to stimulus-induced) flashbacks and other re-experiencing symptoms that occur in severe cases of PTSD.

Anti-convulsants such as carbamazepine and valproate effectively reverse or reduce the kindling (but not necessarily the behavioural sensitization) seen in laboratory animals. With that in mind, several investigators have given these drugs to PTSD patients. Five reports concern carbamazepine and three concern valproate (see Friedman and Southwick, 1995, for references). All studies were open trials or case reports; none were RCTs. In general, carbamazepine reportedly reduced re-experiencing symptoms and insomnia. For example, Lipper et al (1986) observed marked reduction in traumatic nightmares, flashbacks, intrusive recollections and sleep disturbance.

Among the three trials with valproate, Fesler's (1991) is the most extensive. She prescribed valproate because her patients could not tolerate the side-effects of carbamazepine. The surprising finding from this study is that avoidant/numbing and hyperarousal, but not re-experiencing, symptoms responded best to valproate.

Anti-psychotic agents and lithium

Anti-psychotic agents are of interest because: (a) there is some evidence (cited earlier) that dopaminergic systems are altered in PTSD, that PTSD hypervigilance can sometimes be difficult to distinguish from frank paranoia; and that PTSD patients experiencing frequent and intense intrusive symptoms (especially flashbacks) may appear to be psychotic; and (b) because the impulsive and violent behaviour, sometimes seen in

PTSD patients may appear to require chemical restraints. In practice, anti-psychotic agents were heavily prescribed in the 1960s and 70s before PTSD was defined as an anxiety disorder, before clinical reports regarding TCAs and MAOIs were published and before there was any understanding of the pathophysiology of PTSD. The enormous shift in our conceptualization of PTSD during the past 20 years has resulted in neglect of anti-psychotic agents as drugs of choice in PTSD. In fact, there are no published studies on the efficacy of anti-psychotics for this disorder. I have previously proposed (Friedman, 1991) several circumstances in which anti-psychotics might be useful if patients have failed to respond to other classes of drug (especially TCAs, MAOIs, SSRIs or anti-adrenergic agents) mentioned earlier. These indicators are paranoid behaviour, overwhelming anger, aggression, psychotic symptoms, fragmented ego boundaries, self-destructive behaviour and frequent flashback experiences marked by trauma-related hallucinations.

Patients who participated in two open trials with lithium reported reduced autonomic arousal, irritability, anxiety and insomnia. Although lithium appeared to ameliorate hyperarousal symptoms, there was no clear evidence in either trial that core PTSD symptomatology showed improvement (van der Kolk, 1983; Kitchner and Greenstein, 1985).

PHARMACOTHERAPY FOR ACUTE STRESS RESPONSES

Treatment for acutely traumatized individuals has received increased emphasis in recent years. Trauma experts generally believe that rapid intervention, especially within the first 24–72 hours of traumatic exposure, can not only ameliorate immediate psychological symptoms but also prevent the later development of PTSD. Such interventions, generally some variant of critical incident stress debriefing (CISD), have been implemented following natural disasters, sexual assault, military trauma and other catastrophic events (Mitchell, 1983; Milgram, 1986). Despite this growing attention on CISD, there has not as yet been any published research on the clinical indications for pharmacotherapy following acute traumatic events. We (Friedman et al, 1993) have offered a series of recommendations based on our clinical experience and review of literature, although we freely acknowledge that there has not been any systematic evaluation of drug treatment for acute stress responses.

Since it is impossible to predict whether acute post-traumatic symptoms will subside spontaneously or respond favourably to a CISD-type of intervention, we recommend withholding all medication for the first 48 hours, if possible. We recognize that there may be times when severe management problems such as dangerous behaviour, extreme agitation or psychosis may require pharmacological intervention. Here we recommend first, a short-acting benzodiazepine such as lorazepam, and second, a potent non-sedating neuroleptic such as haloperidol.

If severe discomfort persists beyond the first 48 drug-free hours, we recommend sympatholytic and panicolytic agents such as clonidine and

propranolol for patients who exhibit high levels of anxiety and agitation. Patients who exhibit severe dysphoria and avoidant/numbing symptoms will probably benefit more from SSRIs such as fluoxetine and sertraline.

We reiterate that these are merely speculations that have not been evaluated systematically under controlled conditions. It is to be hoped that such evaluations will be conducted in the near future.

CLINICAL QUESTIONS

Is there a single best drug for PTSD?

Although subsequent research may identify a single best drug, no candidate drug is as yet the odds-on favourite. Since only eight RCTs have been published to date, much of our speculation must rely on observations from open trials and case reports. Such an approach is useful, as illustrated by Southwick et al's (1994) quantitative analysis of the MAOI and TCA literature. They reported that MAOI and TCA anti-depressants seemed most effective in reversing re-experiencing but not other symptoms of PTSD. In contrast, early results with SRRIs suggest that these agents may be most useful in reducing avoidant/numbing symptoms. Finally, clonidine and propranolol may be most effective in reducing arousal symptoms, although there is also evidence suggesting that these anti-adrenergic agents may also reduce intrusive symptoms.

Is it appropriate to consider using several drugs concurrently?

Given the neurobiological complexity of PTSD, and given the possibility that different drugs may preferentially affect different clusters of PTSD symptoms, it is reasonable to consider the possibility that carefully selected combinations of drugs might prove more effective than any specific drug on its own. The only published finding to this effect is the observation by Kinzie and Leung (1989) that imipramine plus clonidine was a better treatment for Cambodian refugees with PTSD than was either drug alone. Perhaps each drug had a specific action on a single cluster of PTSD symptoms: imipramine on intrusion and clonidine on arousal. One could extend this argument and speculate that administration of fluoxetine or sertraline might improve therapeutic outcome by an additional increment through a specific SSRI action on avoidant/numbing symptoms. I hasten to caution the reader that these are very premature speculations based on inadequate data that will hopefully spawn some useful research.

Are there contra-indications for certain medications?

An obvious concern is the treatment of PTSD patients with co-morbid alcoholism or substance abuse. On the one hand, such patients would not be candidates for MAOI treatment if they could not abstain from alcohol, cocaine, stimulants or opiates. On the other hand, they would not be

candidates for benzodiazepines if, instead of sticking to the prescribed regimen, they escalated the dose on their own.

Are there concerns about side-effects that are specific for PTSD patients?

A troublesome side-effect is the agitation or anxiety that is sometimes produced in PTSD patients by drugs such as fluoxetine or imipramine. These patients are very sensitive to such side-effects and generally perceive drug-induced anxiety or agitation as an unwelcome or intolerable exacerbation of their original PTSD. Sometimes, they stop medication in the early stages because of this discomfort and will not stick with treatment long enough to see whether they develop tolerance to such side-effects. Propranolol or clonazepam can sometimes control these symptoms and make it possible to conduct an adequate clinical trial.

A related side-effect is drug-induced insomnia sometimes caused by MAOIs or SSRIs. Since so many PTSD patients suffer from a significant sleep disturbance, drug-induced exacerbation of that problem is often considered intolerable. There are anecdotal reports that trazodone, often administered in small (25–100 mg) bed-time doses, is particularly effective in reversing MAOI- or SSRI-induced insomnia.

What do we know about duration of treatment and optimal dose?

Analysis of data from TCA, MAOI and SSRI trials, cited earlier, suggests that clinical trials should last a minimum of 8 weeks and possibly 10–12 weeks on average. There have been no dose–response studies with any drug used in PTSD. Published studies have generally achieved therapeutic results with doses at which those drugs are prescribed for other psychiatric disorders such as depression, obsessive–compulsive disorder and panic disorder.

SUMMARY

Given the neurobiological abnormalities associated with PTSD, it is reasonable to expect that some drug or combination of drugs should provide clinically significant amelioration of symptoms. Patients with PTSD show definite alterations in a number of neurobiological systems that are usually activated when humans are exposed to laboratory or situational stress. This is especially true of the catecholaminergic and HPA systems, although research findings also point to consistent alterations in serotonergic, opioid and thyroid function.

Given such data, it is perhaps surprising that no specific drug or class of drug has yet emerged as the treatment of choice for PTSD. It should be noted, however, that research on clinical pharmacology for PTSD is at an early stage. Only eight randomized clinical trials have been published to date, and only the MAOI phenelzine has been tested more than once.

Promising results have been obtained with TCAs, MAOIs, SSRIs, clonidine, propranolol, carbamazepine and valproate but much more research is needed. It is noteworthy that the current pharmacotherapeutic literature, taken as a whole, suggests that there may not be a broad-spectrum drug that will ameliorate all PTSD symptoms, but rather that different classes of drug may have selective efficacy on specific PTSD core symptoms. For example, MAOIs and TCAs appear selectively to reduce re-experiencing symptoms, SSRIs appear preferentially to affect avoidant/numbing symptoms, and anti-adrenergic agents reduce arousal (and possibly re-experiencing) symptoms. Although it is much too early to give up the search for a single broad-spectrum drug of choice, given the neurobiological complexity of PTSD, it is possible that at some future time, clinical pharmacologists will conclude that it is necessary to treat PTSD with two or three different types of drug simultaneously.

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